Mathematical Modeling Reveals Different Responses to Extrinsic Noise between Parallel and Nonparallel Gene Regulatory Circuits

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1. Introduction

Information flows through channels, everywhere. Your voice on the telephone flows through the wire. Thoughts from distant past flows to you through printed words. The process, nevertheless, is not safe and sound all the time, for noise inevitably gets in the way and the signal is distorted, leaving the receiver at a lost. Anyway, cheer up, it is not that disappointing. Better structure of the information channel gives rise to better performance in handling noise, and the detrimental effects of noise can be minimized.

Gene regulatory circuits are information channels indeed, sensing extrinsic information from the environment or upstream signals and expressing protein products, whose concentration makes the output. How will different circuit structures influence its ability to adjust to extrinsic noise? We embark on a journey to find it out with powerful mathematical modeling tools at hand.

Our team focuses on comparing performance between two ways to get fluorescent protein (EBFP), namely, to express the protein directly from the gene, or to independently express two proteins and let them assembly afterwards to become the same protein as the one in the first way. We see these two alternates as two systems in the view of information theory, the former (system1) as a nonparallel information channel, the latter (system2) a parallel one. Therefore, by analyzing the characteristics of the information channels of two systems, we can easily verify the result from experiment or predict the performance in reality.

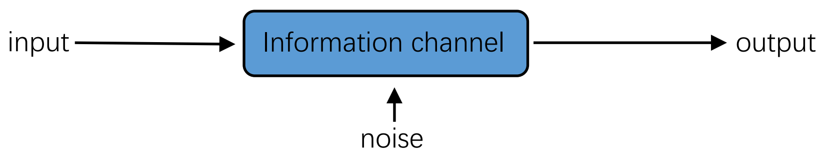


Fig.1—a system in information theory

Beside analyzing the experimental data by calculating channel capacity of two systems (see previous sections), we wanted to know if there are any difference between two systems in amplifying the inputs or responding to the noise. Therefore, we set up the models of two systems. In simulation, different inputs, step signal with or without noise signal in different frequency, were given to both systems. By comparing outputs deriving from two systems, we can get the characteristics of two channels in some aspects of responding to extrinsic noise, thus, may conclude which way of protein synthetic processes has more merit in manufacture.

2. Conclusion of Simulation

When models were set up, we analyzed the features of two systems, using mathematical and informatical methods. By simulation, we draw the conclusion that both system have the

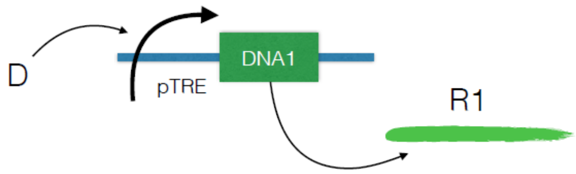
ability to resist influence of extrinsic noise since their low-pass feature. When the noise magnitude is relatively low than input, the first system is more robust than the second system. Thus, we assumed that it reality the amount of input is much larger than noise, so that the amounts of protein synthesized in the direct way by a group of will be more consistent than that in the way with binding process.

However, these conclusions were merely drawn from emulation, and experiments are needed to test them. Besides, we only discussed the influences of one aspect of extrinsic noise, and there are much more details waiting to be studied.

The methods we used in simulation and analyzing details will be discussed below.

3. Reactions and Methods

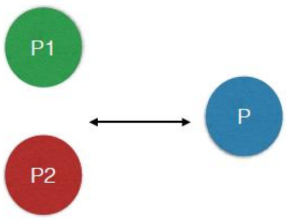
In our experiment, a micro molecule called Dox (D), when bound to rtTA, induces EBPF protein (R1) synthetic through transcription and translation of the gene (DNA1). This process can be simply described by a differential equation in Fig.2 (equation 1), where λ is protein synthetic rate, and d^m is the rate of protein degradation.



$$\frac{d[R1]}{dt} = \lambda\frac{[D]^n}{K+[D]^n} - d^m[R1] \quad \cdots\cdots\cdots(1)$$

Fig.2—the protein synthetic process and its differential equation

In the parallel circuit, the synthetic processes of two parts of protein can also be described as by the equation above with the same parameters. The following process where two proteins (P1 and P2) binds to form one complex (P) can be described by the differential equation in Fig.3 (equation 2), where kon is the rate of protein binding, koff is the protein separating rate, and d^p is the rate of protein degradation. So for the second system, three equations can precisely describe its feature.



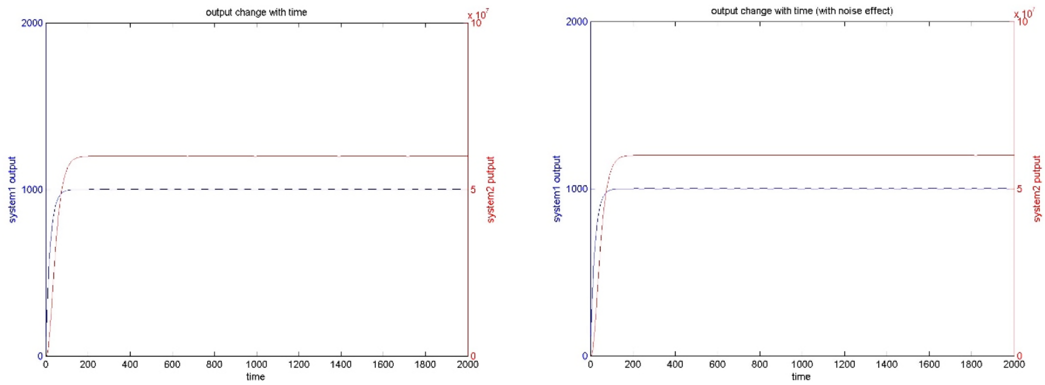
$$\frac{d[P]}{dt} = k_{on}[P1][P2] - k_{off}[P] - d^p[P] \quad \cdots\cdots\cdots(2)$$

Fig.3—the protein binding process in the parallel circuit

4. Simulation

With the ODE models introduced above, we simulated the evolution of the two systems. With the same amount of Dox input, the evolution processes, with and without extrinsic noise,

are shown in Fig.4(a)&(b), where the blue lines represent the results of the first system, meanwhile the red lines represent the ones of the second system (the same afterwards).



(a) (b)

Fig.4—the evolution processes of two systems

Comparing the simulation results of two systems, we find out that with the same amount of Dox inputs, no matter noise is present or not, the outputs of two systems will gradually converge to steady state, but the steady-state values of two systems are rather different: the output value of the second system is about 6*10^4 times larger than that of the first system. However, in our experiment, the output amounts from two systems are relatively coherent. This paradox may owe to the low binding rate in reality, but we assumed it to be 100% in simulation. Besides, we cannot tell the impacts of noise. So in order to compare two systems more precisely, we used two methods, which will be discussed in the next section.

5. Measurement of impacts

To compare the noise impacts of two systems, we compared the steady-state values from different amounts of input (Dox) between them. When no noise included, the relative between the amounts of input and output is shown in Fig.5. We can see from the graph that when the input amount is larger than a threshold, the output amount won't change if inputs increase. When noise signal is added in the inputs, the steady-state values are shown in Fig.6(a), and Fig.6(b) shows the values from the same amounts of Dox input without noise effect. Comparing two graphs in Fig.6, we can easily find out that with noise effect, the steady-state values vary from the ones without noise effect. We assumed the latter ones as standard values. The more the outputs deviate from the standard values, the easier the system be influenced by extrinsic noise. The method to measure and analyze deviation will be discussed below.

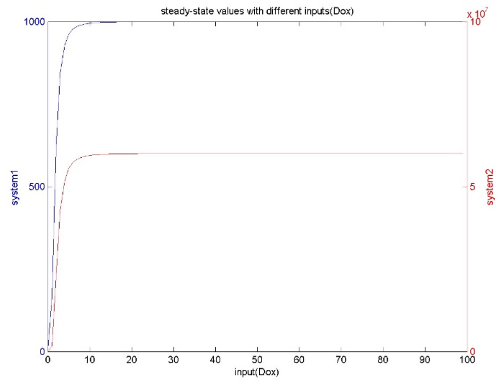
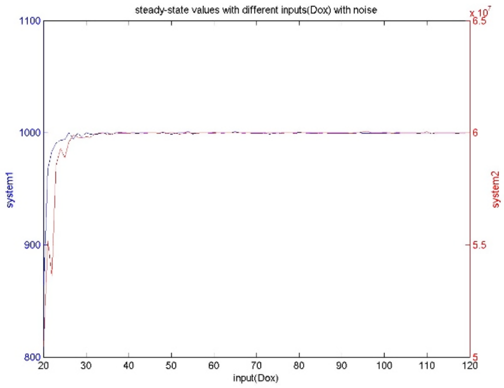
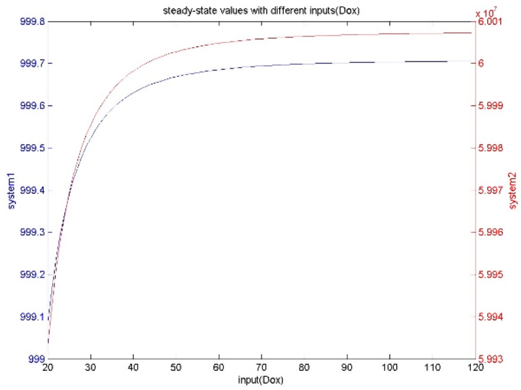


Fig.5—the amount of output change with the amount of input



(a)



(b)

Fig.6—steady-state value change with the amount of input (with noise)

a) Using coefficient of variation (CV)

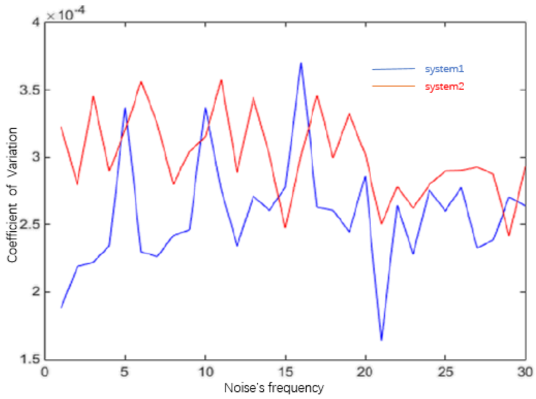
Coefficient of variation's definition is the equation below.

$$\mathrm{CV} = \frac{\sqrt{D(x)}}{E(x)} \qquad \cdots\cdots\cdots \quad (3)$$

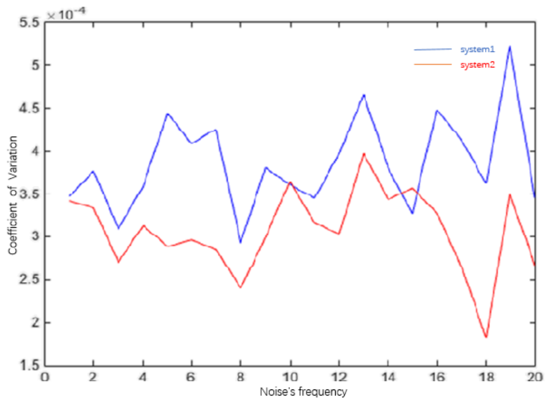
In our model, when the amounts of input vary from x1 to x2, we used the standard values from every xi as f(xi), and the average of f(xi) as E(x) of range (x1, x2). For the steady-state values from inputs with noise, we defined them as g(xi), and D(x) of range (x1, x2) was defined as the equation below (where N is the amount of i in range (x1, x2)).

$$\mathrm{D(x)} = \frac{1}{N}\sum_{i}(g(xi) - f(xi))^2 \qquad \cdots\cdots\cdots \quad (4)$$

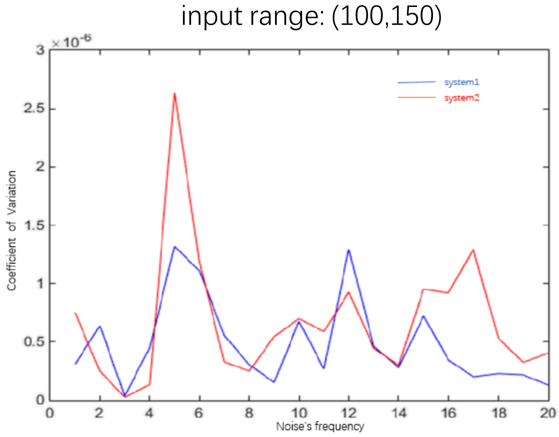
Using equation (3)(4), we can get CVs of outputs from different amounts of Dox input with noise with different intensities and frequencies of two systems, which are shown in Fig.7. The x-axis of the graphs in Fig.7 represents noise frequencies, and y-axis represents the values of coefficient of variations.



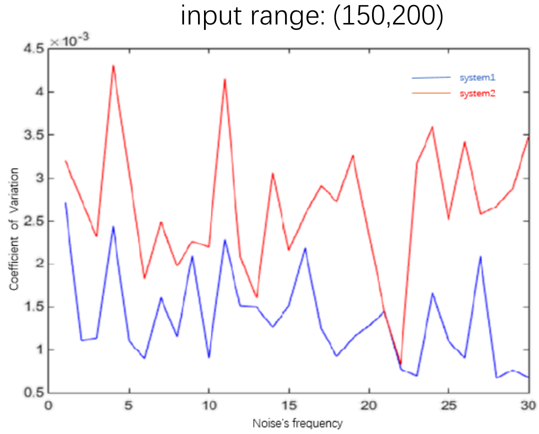
(a) noise magnitude: 50
input range: (100,150)



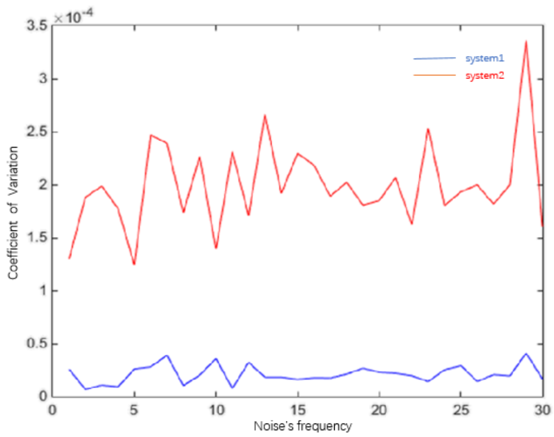
(b) noise magnitude: 50
input range: (150,200)



(c) noise magnitude: 50
input range: (200,250)



(d) noise magnitude: 50
input range: (250,300)



(e) noise magnitude: 50
input range: (300,350)

Fig.7—the CVs of two systems

From Fig.7 we found out that in graph (a)(d)(e), the CVs of the first system are less than of the second system in general, and in graph (b), the CVs of the second system are less than of the first system in general. Besides, in graph (c), the CVs of two systems are generally similar. So we drew the conclusion that when signal-noise ratio (SNR) is between 25% and 30%, the outputs of the second system is less easily influenced by the extrinsic noise added with inputs,

meanwhile, if SNR is higher than 30% or lower than 20%, the first system is more robust than the second system.

Furthermore, we added complex-frequency noise with inputs, which is shown in equation (5), into two systems. The noise magnitude of single-frequency noise component is in the SNR range (25%,30%), which the second system performs better. The coefficient of variations of two systems are shown in Fig.8. The result confirms our judgment that second system is more robust when the SNR is between 25% and 30%.

$$y = 50\sin(noisefre * pi * t) + 50\sin(noisefre * 2 * pi * t) + 50\sin(noisefre * 3 * pi * t) \quad \cdots\cdots\cdots \quad (5)$$

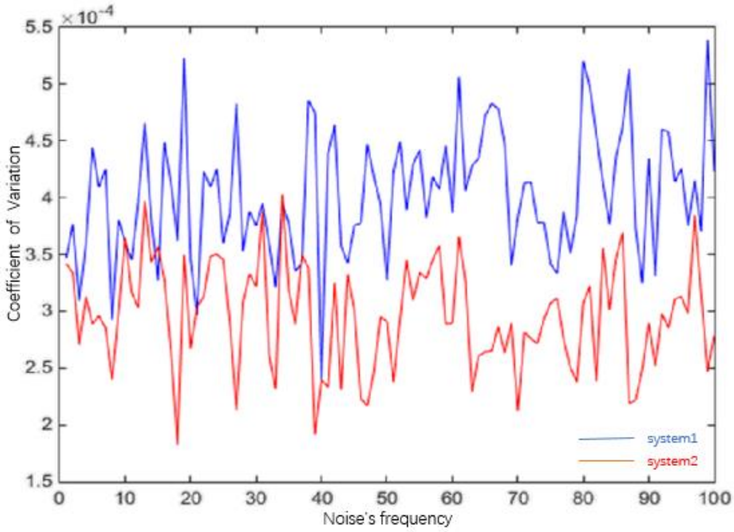
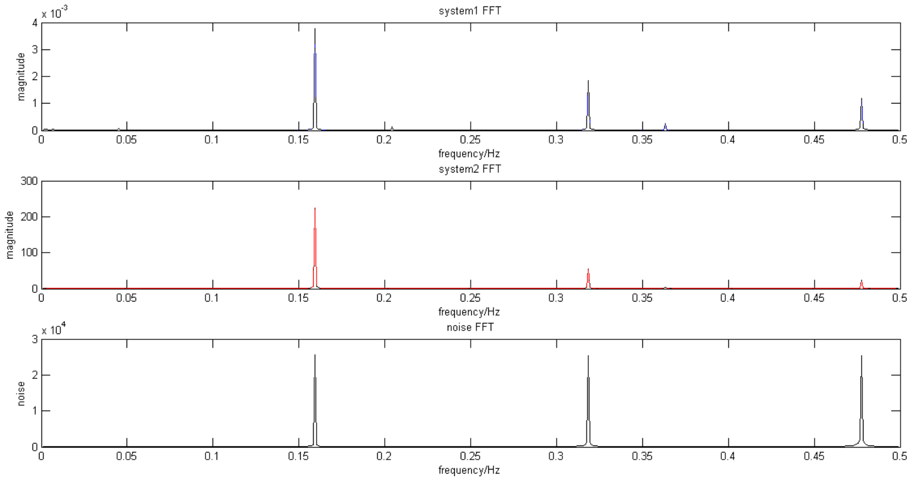


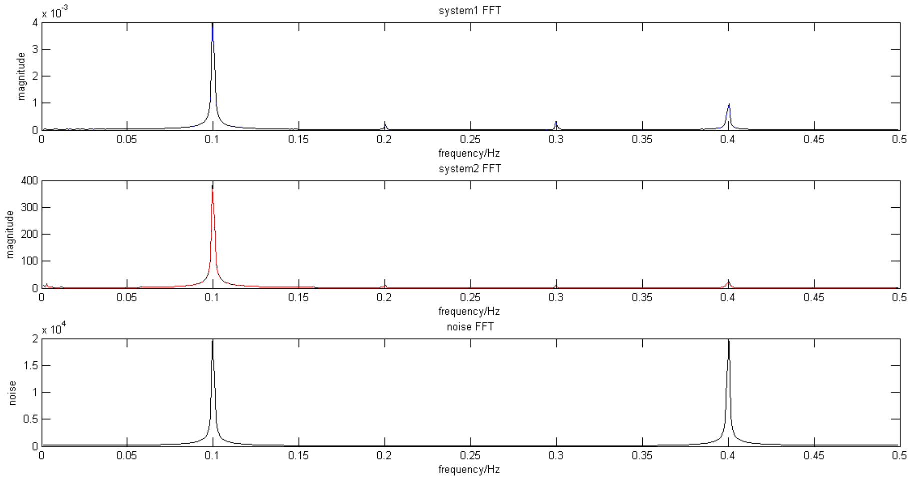
Fig.8 the CVs of two systems (complex-frequency noise effect)

b) Using amplitude-frequency characteristics

In section (a), we discussed the SNR regions in which system1 or system2 is less easily influenced by extrinsic noise. In this section, we will discuss how does noise frequency influence two systems. We used fast Fourier transform (FFT) to analyze the signal's frequencies of noise input and outputs of two channel. In simulation, the Dox input is 500, and the magnitude of every noise component of different frequency is 50. The FFT results of two systems, in which different complex-frequency noise was added with inputs, are shown in Fig.9. The zero-frequency components, which represent steady-state values, are not included in Fig.9.



(a) noise: 50sint+50sin(2t)+50sin(3t)



(b) noise: 50sin(0.2πt)+50(0.8πt)

Fig.9—FFT results of noise and two systems

We can learn from Fig.9 that the higher the noise frequency is, the less easy it will influence the outputs of both systems. Thus, both systems have low-pass characteristic. In reality, noise always has higher frequency than input, so this characteristic makes these systems robust to diminish the impacts of extrinsic noise.

Reference

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